Development of a new treatment for gastritis from natural product

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Introduction

The terms of phytotherapy and phytomedicine were first introduced by the French physician Henri Leclerc (1870-1955). Phytotherapy is defined as the treatment based only on plant material either from the complete plant or extracts used for clinical treatment purposes phytomedicine. In Europe and in North America, almost 25 percent of the active components of currently prescribed medicines were first identified in higher plants. Aspirin (analgesic), vincristine (anticancer), and artemisinin (antimalarial) are representative examples. Over the past twenty years, the interest in medicinal plants has grown enormously in western society and at all levels of society, from the use of herbal products as natural cosmetics and for self-medication by the general public to the scientific investigation of plants for their biological effects in

human beings. The attitude of the pharmaceutical industry on phytomedicine, pharmaceuticals from plants, has also changed. Fifteen years ago almost none of the top 250 companies world-wide had research programs involving plants. Recently, however, over half of them have such programs. WHO estimates that 80 % of the world's population relies on plant-based medicines for primary health care. This focuses the need for research on procedures to test for safety and the efficacy of traditional remedies and to then standardize their effective use.

Gastric mucosal injury can be managed by controlling the balance of two different factors; gastric acid secretion including acid, pepsin, mucosal hypoperfusion, ischemic-reperfusion injury, intramucosal acid-base balance, systemic acidosis, free radicals, bile salts, *Helicobacter pylori* and NSAIDs and gastric mucosal protection including mucosal prostaglandins, mucous bicarbonate barrier, epithelial restitution and regeneration, mucossal blood flow and cell membrane and tight junctions. In Western countries, hyper-acidic condition is considered as a primitive factor for gastric disorders. This is the main reason that physicians in US and Western countries choose the anti-acid secretion drugs such as proton-pump inhibitors (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, etc.) or histamine receptor-$_2$ antagonist (cimetidine, ranitidine, famotidine, nizatidine, roxatidine, etc.) for treatments. On the

other hand, in Asian countries, cytoprotective agents (sucralfate, cetraxate, misoprostol, ornoprostil, rebamipide, teprenone, sofalcone, ecabet sodium, etc) are used for a powerful tool for the clinical treatment of gastric diseases. Both anti-acid and cytoprotective remedies are actually used in many gastric disorders, and are of prime importance in many cases. Western physicians may not be familiar with the use of cytoprotective agents, like the pathogenesis of gastric disorder is not the same from one region to another. For example, in Asian countries including Japan, Korea and China, the degree of acid secretion is not so high as that in Western countries. This phenomenon was explained by the difference in the host and bacterial factors including the prevalence of *Helicobacter pylori* infection. Structural elements of gastric mucosal defense include the mucus and epithelial cell barrier, and physiological elements of protection during the acute phase of the injury involving mucin production, bicarbonate ion secretion and gastric mucosal microcirculation.

DA-9601 (Stillen® capsule)

With its more than 300 species, the genus *Artemisia* is one of the largest in the northern hemisphere. These plants are often dominant in the steppes and semideserts of central Asia, northern Africa and California; and many of them have medicinal and/or

culinary value. For instance, *Artemisia vulgaris* L. (mugwort) is used for flavoring or stabilizing beer, sausage and rice cakes. A tea or compress of mugwort is used to speed labor, expel the afterbirth and promote menstruation and to decreases external inflammation, helps digestion, kills intestinal roundworms and promotes liver detoxification. *A. absinthium* (wormwood) is used to regulate women's menstrual disorders and as a stomachic and sedative. It also stimulates the gallbladder, increases bile flow, eases stomach cramps and stimulates muscle relaxation. The drug is used in the form of an infusion or an alcohol extract. *A. asiatica* Nakai (*Compositae*; local name ssuk, herbal name aeyop) has been frequently used in traditional Asian medicine for the treatment of such diseases as inflammation, cancer and microbial infection. Recently, researchers of Dong-A Pharm. and Natural Products Institute found that the extract of *A. asiatica* possesses gastroprotective effect in experimental gastritis and ulcer models. By fractionation and isolation research, eupatilin (5,7-dihydroxy-3,4,6-trimethoxyflavone), a bioflavone, was determined as an active component. And it was found that eupatilin, the active ingredient, can be obtained not by water extraction but by ethanol extraction and its content varies by the conditions including the place where the plants grow and harvest time. The quality-controlled extract of *A. asiatica* was named DA-9601. DA-9601 possesses antioxidative and anti-inflammatory activities, which contribute to

protective effects against experimentally induced gastric damage.

Pharmacological Effects & Mechanisms of Action

DA-9601 mainly contribute to its protective effects against experimentally induced gastric damage in animal models. DA-9601 evaluated pharmacological effects that gastritis model induced alcohol, compound 48/80 and sodium taurocholate (TCA) in rats (*J Appl Pharmacol*, 4, 111-121, 1996), gastric and duodenal ulcer model caused NSAIDs (indomethacin, aspirin, naproxen), acetic acid and cysteamine (*Arch Pharm Res*, 20, 414-419, 1997) and gastro-esophageal reflux disease model made operation (*Gut*, 49, 364-371, 2001). Also, DA-9601 ameliorated inflammatory bowel disease (*J Appl Pharmacol*, 5, 165-173, 1997; *Int J Colorectal Dis*, 16, 174-181, 2001), pancreatitis (*Pancreas*, 17, 153-157, 1998), liver damage (*Arch Pharm Res*, 21, 508-513, 1998) and liver fibrosis (*Taehan Kan Hakhoe Chi*, 8, 436-47, 2002). DA-9601 confirmed safe drug through acute toxicity study, 4 week repeated oral toxicity study (*J Appl Pharmacol*, 4, 354-363) and general pharmacology (*J Appl Pharmacol*, 4, 174-183).

DA-9601 are known to have antioxidative effect, anti-inflammatory effect, re-epithelization of gastric mucosa and cytoprotective effects, potentially. In antioxidative

and anti-inflammatory effect, DA-9601 inhibited release of leukotriene D_4 on *Helicobacter pylori*-induced in human neutrophils and Kato III cells (*Korean J Physiol Pharmacol*, 1, 573-580, 1997) and xanthine oxidase activity on ethanol-induced gastropathy in rats (*J Ethnopharmacol*, 88, 269-273, 2003). DA-9601 decreased reactive oxygen species (ROS) formation, LDH, myeloperoxidase (MPO) activity, maloedialdehyde (MDA), *i*NOS activity, IL-1β and IFN-γ. However, DA-9601 increased glutathione peroxidase activity, reduced glutathione contents, heat shock protein (HSP) 70 and IL-10 level. In relation to quality of ulcer healing (QOUH), DA-9601 established acceleration of gastric mucosa re-epithelization on acetic acid–induced chronic gastric ulcer model, compared to other cytoprotectants. Finally, in cytoprotective effect, DA-9601 augmented secretion of mucus, mucin and prostaglandin E_2, dose-dependent manner.

Recently, DA-9601 evaluated chemopreventive effect in human promyelocytic leukemia cells (*Mutations Res*, 496, 191-198, 2001) and on phorbol ester-induced ornithine decarboxylas activity, papilloma formation, COX2 expression, *i*NOS expression and NF-┤ B activation in mous skin (Int J Cancer, 100, 456-462, 2002).

Clinical Trial Study

Phase III clinical trial study was to assess the efficacy of DA-9601 (Stillen® capsule) for the treatment of erosive gastritis. Five hundred and fifty patients with erosive gastritis were enrolled and divided into three groups in study multicenter, double-blind comparative study. Each group received 180mg of DA-9601 or 600mg of cetraxate (Neuer® capsule) t.i.d. for 2 weeks, respectively and followed up by endoscopic examination for evaluation. Patients treated with 180mg of DA-9601 had a significantly improved endoscopic cure rate of gastritis (55.6%, respectively) compared with patients treated with 600mg of cetraxate (35.5%, $p < 0.001$). Endoscopic improvement rate was also significantly higher in 180mg group (67.3%) of DA-9601 treated patients than cetraxate treated group (46.4%, $p < 0.001$).

Conclusion

These results clearly demonstrate that DA-9601 (Stillen® capsule) is an efficacious, safe, and well-tolerated treatment for gastritis.